

REMARKS

I. Status Summary

Claims 44, 47, 48, and 51-55 are pending in the current application and have been examined. Claims 44, 47, 48, and 51-55 remain rejected under 35 U.S.C. § 112, first paragraph, upon the contention that these claims failed to comply with the written description and enablement requirements of 35 U.S.C. § 112, first paragraph.

Claims 44, 47, 48, and 51-55 have been subjected to a series of rejections under 35 U.S.C. § 112, second paragraph, upon the contention that the claims are indefinite.

Claims 44, 47, 48, and 52-55 remain rejected under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by Chang *et al.* (1995, *Cell Biol. Intl*, Vol 19, pg. 143-149; hereinafter "Chang 1995") or by Chang *et al.* (1997, *Cell Biol Intl*, 21:495-499; hereinafter "Chang 1997").

Claims 44, 47, 48, and 51-55 remain rejected under 35 U.S.C. § 102(e) upon the contention the claims are anticipated by U.S. Patent No. 5,340,740 (hereinafter "the '740 Patent"); U.S. Patent No. 5,656,479 (hereinafter "the '479 Patent"); or U.S. Patent No. 5,840,510 (hereinafter "the '510 Patent").

Claims 44, 47, 48, and 51-55 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 8-10 of the '740 Patent, claim 1 of the '479 Patent or the '510 Patent, or claims 1-12 of the '659 Patent, each in view of Chang 1995.

Claim 44 has been amended. Support for the amendments can be found throughout the specification of the application as filed, including particularly at page 6, lines 9-13, and on page 7, lines 19-24. Additional support for the amendments can be found on page 13, line 21, through page 14, line 4, in Figures 3 and 4, and in Examples 2-4.

New claims 56-57 have been added. Support for the new claims can be found throughout the specification of the application as filed, including particularly at page 4, lines 10-17. Additional support for the amendments can be found on page 5, line

Serial No.: 09/757,054

16, through page 7, line 24 (Brief Description of the Drawings), at page 12, lines 3-4, in Figures 1-4, and in Examples 1-4.

No new matter has been added by virtue of the claim amendments or the addition of the new claims. Reconsideration of the application as amended and based on the remarks set forth below is respectfully requested.

II. Response to the Rejections under 35 U.S.C. § 112, First Paragraph

II.A. Response to the Written Description Rejection

Claims 44, 47, 48, and 51-55 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the subject matter was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

After careful consideration of the rejection and the Patent Office's bases therefor, applicants respectfully traverse the rejection and submit the following remarks.

On page 1 of the pending Official Action, the Patent Office states that claims 44, 47, 48, and 51-55 remain rejected under the written description requirement of 35 U.S.C. § 112, first paragraph. However, all of the aspects of the previously presented rejection appear to have been withdrawn with the exception of a new matter rejection of claims 53 and 54. Accordingly, applicants respectfully submit that the instant rejection is not applicable to claims 44, 47, 48, 51, 52, and 55. As a result, applicants will address the new matter rejection of claims 53 and 54, and respectfully submit that it is applicants' understanding that the rejections of the other claims have been withdrawn.

The new matter rejection of claims 53 and 54 has been maintained from the previous Official Action. In response to that Official Action, applicants argued that page 13, line 21, through page 14, line 7, of the specification disclosed a sustained culture of undifferentiated avian cells expressing an embryonic stem cell phenotype

wherein the embryonic stem cell phenotype is maintained for at least one month.

This section of the specification is presented below:

In a preferred embodiment, avian embryonic gonadal cells comprising primordial germ cells from a four to five day incubated avian embryo are seeded onto the preconditioned feeder matrix with conditioned media, and the avian cells give rise to nests or colonies of cells exhibiting an embryonic stem cell phenotype. Unlike the case with mammalian stem cells, it is currently preferred to have a preconditioned feeder matrix to facilitate the survival and development of avian PGCs into undifferentiated avian cells expressing an ESC phenotype. The avian embryo cells of the present invention can be cultured for at least one or two months as is typical for a primary cell culture, which is significantly greater than the usual two week life of primary cultures of cells from an unincubated avian embryo.

Specification at page 13, line 21, to page 14, line 7. According to the Patent Office, this passage:

merely states that PGCs are maintained for one or two months. The specification did not teach or suggest that cells having an ES cell phenotype were maintained in culture for one or two months and does not explicitly or implicitly suggest that the ES cell phenotype is maintained for one or two months as claimed. The specification did not teach or suggest the ES cell phenotype was maintained in culture for one to two months as claimed.

Official Action at page 4.

Applicants respectfully disagree. Careful review of the paragraph reveals that the phrase “[t]he avian embryo cells of the present invention can be cultured for at least one or two months as is typical for a primary cell culture” is preceded by the sentence “[u]nlike the case with mammalian stem cells, it is currently preferred to have a preconditioned feeder matrix to facilitate the survival and development of avian PGCs into undifferentiated avian cells expressing an ESC phenotype” (emphasis added). Applicants respectfully submit that the juxtaposition of these two sentences, particularly without separating them by beginning a new paragraph, makes it clear that the culturing of the cells is intended to produce undifferentiated

avian cells expressing an ESC phenotype, and that the ESC phenotype is present in the culture for at least one or two months.

Given the nature of the specification as a whole, applicants further respectfully submit that the disclosure is directed to the production of colonies of undifferentiated avian cells (*i.e.* cells expressing an ESC phenotype). If the cells that were in culture for at least one or two months did not maintain an ES cell phenotype (*i.e.* an undifferentiated state), there would have been no motivation for disclosing the fact that they could be maintained in culture for this time period.

Even assuming that the Patent Office's interpretation of the specification encompasses one possible interpretation, according to the Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, ¶1, "Written Description" Requirement (hereinafter "the Written Description Guidelines"), there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. Applicants respectfully submit that the Patent Office's asserted interpretation of the passage does not suffice to overcome the strong presumption of adequacy of the written description. The Patent Office has not pointed to any part of the specification that excludes the interpretation maintained by applicants.

Applicants respectfully submit that a strong presumption cannot be overcome simply by pointing out another possible interpretation. The Patent Office has not presented clear and convincing evidence that the specification as filed does not support the subject matter of claims 53 and 54. Accordingly, applicants respectfully submit that the Patent Office has not presented a proper written description rejection of claims 53 and 54.

Applicants further respectfully submit that the application of the instant rejection to claims 44, 47, 48, 51, 52, and 55 has not been articulated by the Patent Office, and thus the rejection as to those claims is believed to have been addressed in the prior Amendment and Remarks. Accordingly, applicants respectfully request the withdrawal of the rejection with respect to claims 44, 47, 48, and 51-55, and the allowance of these claims at this time.

II.B. The Enablement Rejection

Claims 44, 47, 48, and 51-55 remain rejected under 35 U.S.C. § 112, first paragraph, upon the contention that while the specification is enabling for a culture comprising PGCs and avian feeder cells, the specification does not reasonably provide enablement for culturing PGCs having an ES cell phenotype for at least one or two months as broadly claimed. The Patent Office bases this rejection on the following assertions:

- neither the art nor the specification teaches how to culture avian PGCs in the presence of avian feeder cells for one or two months.
- the specification does not teach the amounts of essential growth factors that were required to culture avian PGCs in the presence of feeder cells for one or two months.
- the specification does not teach the stage of isolation and culture conditions required to maintain chicken ES cells for at least a month.
- the specification does not teach the stage and conditions required to obtain ES cells in species other than chickens.
- it would have required undue experimentation to isolate any avian ES cell other than chicken ES cells or to maintain any ES cell for one or two months as claimed.

After careful consideration of the rejection and the Patent Office's bases for the rejection, applicants respectfully traverse the rejection and submit the following remarks.

According to the Patent Office, the Ponce de Leon reference of record (1997, Revista Brasileira de Reproducao Animal, Vol. 21:96-101; hereinafter "Ponce de Leon"), teaches that LIF, bFGF, IGF, and SCF are required for long term culture of avian PGCs. Thus, the Patent Office appears to conclude that because Ponce de Leon discloses a culture with LIF, bFGF, IGF, and SCF, any subsequent claims to avian ES cell culture would have to disclose the amounts of these "essential growth factors".

In order to comply with the enablement requirement of § 112, first paragraph, the specification as filed must enable one of ordinary skill in the art to make and use the invention commensurate with the scope of the claims. Applicants respectfully submit that it has never been a requirement that a patent specification must prove or disprove what is at the time considered the state of the art. Applicants respectfully submit that isolating and culturing gonadal cells as taught in Examples 1-4 of the instant specification results in a sustained culture of undifferentiated avian cells that maintain an ES cell phenotype for at least one or two months. Applicants have shown that it is not required that exogenous LIF, bFGF, IGF, or SCF be added to the culture in order for this to occur.

Even assuming *arguendo* that one or more exogenous growth factors were required under the culture conditions of Ponce de Leon, applicants respectfully submit that this is irrelevant. The conditions under which these factors are necessary in Ponce de Leon are not disclosed in any meaningful detail in the cited reference. For example, Ponce de Leon does not disclose what media was used to grow the cells. It also does not teach such conditions as the number of feeders used per culture vessel, the number of PGCs seeded, etc. Thus, applicants respectfully submit that it is not possible to determine from the Ponce de Leon reference under what conditions the use of LIF, bFGF, IGF, and SCF is necessary.

In contrast, applicants respectfully submit that the instant application provides sufficient detail as to relevant stage of isolation and culture conditions that can be employed for long term culture of avian PGCs. For example, the specification discloses that PGCs can be isolated from the gonad and genital ridge from later than stage 14 (H&H) chickens. This explicitly discloses the stage of isolation. Additionally, Figure 1 depicts the influence of the number of STO feeder cells on PGC growth and maintenance; Figure 2 demonstrates the influence of preconditioning of the feeder matrix; and Figure 3 shows the combined effects of the number of STO cells used and the numbers of gonadal cells initially seeded per well. Applicants respectfully submit that these results, in combination with the other disclosure found within the instant application, provide adequate information for one

of ordinary skill in the art to establish and maintain undifferentiated avian cells expressing an embryonic stem cell phenotype from PGCs. Applicants further respectfully submit that once undifferentiated avian cells expressing an embryonic stem cell phenotype are established, these same culture conditions are sufficient to maintain the cells in an undifferentiated state. Applicants therefore respectfully submit that by following the disclosure of the specification, one of ordinary skill in the art would be able to grow and maintain PGCs and avian feeder cells for one or two months without undue experimentation.

The Patent Office asserts that "Ponce de Leon need not be fully enabling to establish that these growth factors were essential to sustaining PGC cultures as claimed and that the amount of growth factors required to sustain PGCs for one or two months as claimed was unknown. Ponce de Leon need not teach the amounts of growth factors used to sustain PGC cultures to establish the state of the art at the time of filing". Official Action at page 6. Applicants respectfully traverse these assertions as reciting a context for an enablement determination that is improper and unsupported by any cited authority.

According to the Court of Appeals for the Federal Circuit, the proper inquiry is whether the specification as filed teaches how to make and use the invention. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988); *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."). Since following the teachings in the specification leads one of skill in the art to be able to make and use the invention, the specification is by definition enabling. Why the culture conditions work, or how they differ from what was then the state of the art need not be explicitly disclosed. See e.g., *Newman v. Quigg*, 877 F.2d 1575, 1581, 11 USPQ2d 1340, 1345 (Fed.Cir.1989) (noting that "it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works"). Thus, applicants respectfully submit that how or why the culture works in light of the prior art is not relevant, as what is

important is that the invention works and that the specification teaches the skilled artisan how to make and use it.

Continuing with the instant rejection, the burden is on the Patent Office to establish that it would have required one of ordinary skill in the art undue experimentation to prepare any undifferentiated avian cell expressing an embryonic stem cell phenotype other than chicken cells, and applicants respectfully submit that Patent Office has not met this burden. According to the Patent Office, "different avians have different stages and the culture conditions required to culture PGCs isolated from different species varies". Official Action at page 7.

Initially, applicants specifically disagree with the Patent Office's contention that "different avians have different stages". There is no scientific support provided for this contention, and it is contrary to the knowledge of the skilled embryologist. Applicants respectfully submit that all avians undergo essentially the same stages of development, and that the only difference might be the timing of each stage (an element that applicants respectfully submit is easily determined by the skilled artisan through routine experimentation for any avian species). With regard to the stage of isolation for isolating genital ridge or gonadal PGCs, applicants respectfully submit that the specification discloses that the appropriate stage is after stage 14 on the Hamburger & Hamilton staging system. Alternatively, the stage is described as after formation of the primitive streak (*i.e.* post-gastrulation). Applicants respectfully submit that each of these developmental stages are adequately known to one of ordinary skill in the art, and the applicability of these stages to avian species other than chickens is clearly understood to the ordinary artisan. Thus, applicants respectfully submit that the stage of isolation is explicitly disclosed in the specification, and that this description is equally applicable to other avian species as it is to chickens.

The Patent Office further asserts that the parameters required to obtain undifferentiated avian cells expressing an embryonic stem cell phenotype in non-chicken avians were not within the realm of routine experimentation for one of ordinary skill in the art at the time that the invention was made. Again, the Patent

Office points to no specific authority to support this contention. Additionally, this does not take into account the teachings of the instant specification where indeed undifferentiated avian cells expressing an embryonic stem cell phenotype were produced from chicken embryos. Thus, while the working examples of the present U.S. patent application pertain to chicken embryos, it is respectfully submitted that the guidance provided in the present U.S. patent application as filed would provide for the development of ES cells from other avian species, including turkeys, ducks, geese, quails, and pheasants.

Accordingly, applicants respectfully submit that the Patent Office has not met its burden in asserting that claims 44, 47, 48, and 51-55 do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph. As a result, applicants respectfully request that the rejection of these claims under 35 U.S.C. § 112, first paragraph, be withdrawn, and the claims allowed at this time.

III. Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 44, 47, 48, and 51-55 have been rejected on several bases under 35 U.S.C. § 112, second paragraph, upon the contention that certain terms and phrases appearing in the claims are unclear. Applicants have considered the individual rejections and the bases therefor, respectfully traverse the rejections, and submit the following.

The first basis for rejection rests on the Patent Office's assertion that the phrase "undifferentiated avian cells expressing an embryonic stem cell phenotype" is unclear (claim 44). According to the Patent Office, "it is unclear if the cells merely share a phenotype in common with avian ES cells or if the cells are avian ES cells". Official Action at page 11.

Applicants initially note that the Court of Appeals for the Federal Circuit has repeatedly stated that absolute precision is not required to adequately define the metes and bounds of the claims of a patent application. "Section 112, ¶2, requires only reasonable precision in delineating the bounds of the claimed invention." *U.S. v. Teletronics, Inc.*, 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988), *cert. denied*, 490 U.S.

1046 (1989) (citation omitted) (emphasis added). The Court of Appeals for the Federal Circuit has also clarified the test for the definiteness of a claim: “[t]he test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more”. *Miles Laboratories, Inc. v. Shandon, Inc.*, 27 U.S.P.Q.2d 1123, 1126 (Fed Cir. 1993), *cert. denied* 510 U.S. 1100 (1994) (citations omitted).

Applicants respectfully submit, and the Patent Office concedes, that the above-noted phrase is specifically defined in the specification. Applicants further respectfully submit that the phrase refers to cells with a certain morphology that those of skill in the embryonic stem cell art recognize as being characteristic of ES cells and ES-like cells: namely, a large nucleus, a prominent nucleolus, and little cytoplasm. See Specification at page 9, lines 5-6. Thus, applicants respectfully submit that the phrase at issue would be understood by the skilled artisan, and therefore respectfully request that the instant rejection be withdrawn at this time.

The Patent Office next contends that the definition of “embryonic stem cell phenotype” is unclear because the phrase “refers to” on page 9, line 4, “makes the citation unclear because it cannot be determined if ‘refers to’ is intended to define the phenotype or merely to describing to what the phenotype is relevant”. Official Action at page 8. The Patent Office continues to cite other passages from the specification that it alleges renders the phrase unclear. However, applicants respectfully submit that the Patent Office has adopted an improper standard for measuring claim terminology under the second paragraph of § 112. The correct standard is not whether certain phrases taken from isolated sections of the specification can be interpreted in contradictory ways, but whether the specification taken as a whole adequately informs the skilled artisan as to the metes and bounds of the claims. Applicants respectfully submit that the instant specification clearly meets this standard.

Accordingly, applicants respectfully submit that the instant aspect of the rejection under the second paragraph of § 112 has been addressed.

The Patent Office next asserts that it remains unclear how PGCs isolated from an embryo later than stage 14 are distinguished from PGCs isolated from a stage X or a stage 14 embryo. According to the Patent Office, PGCs isolated from stage X, 14, and after stage 14 have the same structure and function.

Applicants respectfully submit that the Patent Office contention that PGCs isolated from stage X, stage XIV, stage 14, or after stage 14 have the same structure and function has not been supported by competent scientific authority as is required for any statement for which the Patent Office takes official notice. Additionally, applicants respectfully submit that the Patent Office's assertion is contrary to the understanding of those of skill in the art at the time of filing because prior to the disclosure in applicants' specification, it was not believed to be possible to provide a sustained culture of undifferentiated avian cells that could be derived from PGCs isolated from a later than stage 14 embryo.

As such, applicants respectfully submit that those of skill in the art believed that the structure and function of PGCs did not have the same structure and function of PGCs isolated prior to this stage. Indeed, it was believed that PGCs isolated from later than stage 14 embryos had already initiated commitment to terminal differentiation into germ cells. Accordingly, the Patent Office's beliefs to the contrary are insufficient to support a rejection under § 112, second paragraph.

Applicants respectfully submit that the claim terminology itself is absolutely clear: avian primordial germ cells and stromal cells isolated together from the embryonic genital ridge or gonad from an avian embryo at a stage later than stage 14 according to the Hamburger & Hamilton staging system. Thus, given that the language of the claim itself is clear, the asserted basis for the instant rejection does not support a rejection under the second paragraph of § 112.

In summary, applicants respectfully submit that the rejections of claims 44, 47, 48, and 51-55 under 35 U.S.C. § 112, second paragraph, have been addressed, and that the claims are in condition for allowance at this time. Applicants respectfully solicit a Notice of Allowance as to claims 44, 47, 48, and 51-55.

IV. Rejections under 35 U.S.C. § 102

IV.A. Rejection in view of Chang 1995

Claims 44, 47, 48, and 52-55 have been rejected under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by Chang 1995. According to the Patent Office, Chang 1995 taught making feeder cells by isolating cells from the genital ridge of day 5 embryos and culturing the cells for 4 days. The Patent Office further asserts that the feeder cells are “preconditioned” because they are in culture for 4 days prior to the addition of day 2 PGCs, that the feeder cell media is “conditioned” because it contains biologically active components obtained from the previous 4 days in culture prior to adding day 2 PGCs, and that the cells isolated from the genital ridge comprised stromal cells and PGCs as claimed. Applicants have carefully considered the rejection and the Patent Office's bases therefor, and respectfully traverse the rejection as follows.

Applicants respectfully submit that Chang 1995 does not anticipate the instant claims because Chang 1995 does not disclose each and every element of the claims. Specifically, Chang 1995 does not disclose the production of a sustained culture of one or more colonies of undifferentiated avian cells produced by isolating PGCs and stromal cells together from an embryo later than stage 14. Rather, Chang 1995 discloses isolating day 5 chicken cells that are made into feeders, and later isolating day 2 PGCs (and stromal cells) from chickens. Thus, the chicken PGCs disclosed in Chang 1995 are day 2, not “later than stage 14” as recited in the instant claims. Stage 14 in the H&H staging system corresponds to the 23 somite stage, which does not occur until about 50-54 hours of development in chickens (*i.e.* day 3). See page 56 of Hamburger & Hamilton, 1951 (88 *J Morphol* 49-92; reprinted as page 238 of 195 *Devel Dynam* 231-272 (1992), a copy of which attached; hereinafter referred to as “Hamburger & Hamilton”). Thus, “later than stage 14 according to the Hamburger & Hamilton staging system” excludes “day 2”. Accordingly, Chang 1995 does not disclose each and every element of claim 44.

Furthermore, Chang 1995 does not disclose a sustained culture comprising one or more colonies of undifferentiated avian cells at all. Rather, applicants

respectfully submit that Chang 1995 discloses culturing PGCs for several days, which are then transferred into chicken embryos where they colonize the gonad of the recipient chicken. Stated another way, Chang 1995 discloses removing PGCs, culturing them in the short term, and returning them to a recipient where they colonize the gonad. Since PGCs normally colonize the gonad, Chang 1995 does not disclose a change in either the phenotype or behavior of the isolated cells.

In contrast, the instant specification discloses isolating PGCs, which are relatively large, granular cells, and growing them in culture to produce colonies of undifferentiated cells, each individual cell of which is characterized by having a large nucleus, a prominent nucleolus, and little cytoplasm. See Specification at page 9, lines 5-6. This is a significant difference from the teachings of Chang 1995. The cited reference teaches a short-term culture of PGCs, whereas the instant specification teaches a long-term culture of undifferentiated cells derived from PGCs.

Since Chang 1995 does not disclose each and every element of claim 44, applicants respectfully submit that Chang 1995 does not anticipate claim 44. Claims 47, 48, and 52-55 all depend directly or indirectly from claim 44, and thus include all the elements of distinguished claim 44. Accordingly, applicants respectfully request the withdrawal of the rejection of claims 44, 47, 48, and 52-55 in view of Chang 1995, and respectfully request a Notice of Allowance to that effect.

IV.B. Rejection in view of Chang 1997

Claims 44, 47, 48, and 52-55 have been rejected under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by Chang 1997. According to the Patent Office, Chang 1997 teaches isolating germinal ridge stromal cells from stage 27-28 embryos, which were then cultured for 5 days in media containing IGF, FGF, and LIF with germinal ridge stromal feeder cells isolated from day 5 embryos to obtain gPGCs. Applicants have carefully considered the rejection and the Patent Office's bases therefor, and respectfully traverse the rejection as follows.

Applicants respectfully submit that Chang 1997 does not anticipate the claims because the cited reference does not disclose every element of the claims. As noted above, claim 44 recited a sustained culture of undifferentiated avian cells comprising

a preconditioned feeder matrix; conditioned media; and avian primordial germ cells and avian stromal cells, wherein the avian primordial germ cells and stromal cells are isolated together from the embryonic genital ridge or gonad from an avian embryo at a stage later than stage 14 according to the Hamburger & Hamilton staging system and grown in the sustained culture to produce one or more colonies of undifferentiated avian cells.

Applicants respectfully submit that the arguments presented hereinabove with respect to the Chang 1995 reference are equally applicable to the instant rejection. In particular, Chang 1997 does not teach a culture that comprises one or more colonies of undifferentiated avian cells. Rather, Chang 1997 teaches the short-term (*i.e.* 5 day) culture of chicken PGCs. At 5 days, colonies of undifferentiated avian cells are not produced. This is clearly pointed out on page 496 of Chang 1997, wherein it is states that "[a]fter 5 days in culture, the gPGCs landing on primary cultured GRSCs were suspended by gentle pipetting without using digestive enzymes". Chang 1997 at page 496 (emphasis added). As one of ordinary skill in the art would recognize, gentle pipetting without the use of digestive enzymes would not release colonies of undifferentiated cells.

Thus, the cells disclosed in Chang 1997 are simply PGCs. Accordingly, like Chang 1995, Chang 1997 only discloses expanding PGC numbers in culture, and that when the PGCs are reintroduced into avian embryos they behave just like normal PGCs: they colonize the gonad. Stated another way, Chang 1997 teaches a method of culturing PGCs to produce an increased number of PGCs. This is unlike the sustained culture of claim 44, wherein colonies of undifferentiated avian cells derived from PGCs are produced.

Since Chang 1997 does not disclose each and every element of claim 44, applicants respectfully submit that Chang 1997 does not anticipate claim 44. Claims 47, 48, and 52-55 all depend directly or indirectly from claim 44, and thus include all the elements of distinguished claim 44. Accordingly, applicants respectfully request the withdrawal of the rejection of claims 44, 47, 48, and 52-55 in view of Chang 1997, and respectfully request a Notice of Allowance to that effect.

IV.C. Rejection in view of the Petite Patents

Claims 44, 47, 48, and 52-55 have been rejected under 102(e) as being anticipated by U.S. Patent Nos. 5,340,740; 5,656,479; or 5,840,510 (hereinafter collectively referred to as “the Petite Patents”). According to the Patent Office, the Petite Patents teach culturing cells from a stage X embryo and isolating PGCs (‘740 Patent). The cells were seeded onto chicken embryonic fibroblast feeder layers and cultured with BRL conditioned medium. The Patent Office asserts that “PGCs isolated from stage X are equivalent to PGCs isolated later than stage 14 as claimed because PGCs isolated from stage X and XIV have the same function”. See Official Action at page 19 (emphasis added). Applicants have carefully considered the rejection and the Patent Office’s bases therefor, and respectfully traverse the rejection as follows.

Applicants respectfully submit that the Petite Patents do not disclose each and every element of the present claims. Specifically, the Petite Patents do not disclose the use of PGCs isolated from the gonad or genital ridge of an avian embryo at a stage later than stage 14, or the production of a sustained culture comprising *inter alia* colonies of undifferentiated avian cells.

Applicants direct the Patent Office’s attention to the discussion above regarding the assertion that the structure and function of cells isolated from stage X as described by the Petite Patents are the same as those of cells isolated from stage 14 as claimed. The Patent Office has articulated no scientific basis for this assertion, and further it is respectfully submitted that this assertion is directly contrary to the weight of the knowledge in the field that later than stage 14 PGCs were committed to terminal differentiation.

Furthermore, applicants respectfully submit that the Patent Office’s assertion that the Petite Patents disclose that “PGCs and stromal cells were inherently ‘isolated together from the embryonic genital ridge or gonad’ as claimed because the whole embryo was isolated and inherently contained both PGCs and stromal cells in the genital ridge or gonad” is clearly inaccurate because stage X embryos have neither a genital ridge nor a gonad.

To elaborate, there are two main art-recognized staging systems, the Eyal-Giladi and Kochav (EG&K; from Eyal-Giladi and Kochav, 1976, *Dev. Biol.* 49(2):321-37) staging system and the Hamburger and Hamilton (H&H; from Hamburger and Hamilton) staging system. The former uses Roman numerals, and the latter Arabic numerals. The EG&K system relates to those stages prior to formation of the primitive streak, whereas stage 1 of the H&H system begins after the late cleavage stage. See page 54 of Hamburger & Hamilton, 1951 (88 *J Morphol* 49-92; reprinted as page 236 of 195 *Devel Dynam* 231-272 (1992)). The avian embryos disclosed in the Petitte Patents are all staged according to the EG&K staging system, wherein stage IX through stage XIV embryos are disclosed. Thus, the Petitte Patents do not disclose the isolation of PGCs from later than stage 14 (H&H) embryos as recited in claim 44. Additionally, the PGCs of claim 44 are isolated along with stromal cells from the embryonic gonad or genital ridge, structures that are not present in the stage X or XIV avian embryo.

Since the Petitte Patents do not disclose each and every element of claim 44, applicants respectfully submit that the Petitte Patents do not anticipate claim 44. Claims 47, 48, and 52-55 all depend directly or indirectly from claim 44, and thus include all the elements of distinguished claim 44. Accordingly, applicants respectfully request the withdrawal of the rejection of claims 44, 47, 48, and 52-55 in view of the Petitte Patents, and respectfully request a Notice of Allowance to that effect.

V. Double Patenting Rejections

V.A. Rejection based on U.S. Patent No. 5,340,740 in view of Chang 1995

Claims 44, 47, 48, and 51-55 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 8-10 of U.S. Patent No. 5,340,740 (hereinafter "the '740 Patent") in view of Chang 1995. According to the Patent Office:

Claims 1 and 8-10 claim a sustained culture of undifferentiated avian cells having an ES cell phenotype and methods of making such a

culture. '740 did not claim culturing the cells on avian feeder cells or the cell culture made by the method.

However, at the time of filing, Chang taught culturing PGCs on avian stromal cells. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to isolate avian cells having an ES cell phenotype as taught by '740, wherein the avian cells are cultured on avian feeder cells. One of ordinary skill in the art at the time the invention was made would have been motivated to use avian feeder cells to increase the number of PGCs as taught by Chang (abstract).

Official Action at page 16. Applicants have carefully considered the rejection and the Patent Office's bases therefor, and respectfully traverse the rejection as follows.

Applicants respectfully submit that the combination of the '740 Patent and Chang 1995 does not suffice to create a *prima facie* case of obviousness. Particularly, each and every element of the presently claimed invention is not disclosed in the cited references, the cited references in fact teach away from the claimed combination, and thus one of ordinary skill in the art would not have been motivated to combine the cited references to arrive at the instantly claimed invention.

Applicants respectfully submit that the claimed invention recites a sustained culture that comprises a preconditioned feeder matrix, conditioned medium, and avian primordial germ cells and avian stromal cells, wherein the avian primordial germ cells and stromal cells are isolated together from the embryonic genital ridge or gonad from an avian embryo at a stage later than stage 14 according to the Hamburger & Hamilton staging system and grown in the sustained culture to produce one or more colonies of undifferentiated avian cells. As discussed hereinabove, the Chang 1995 reference does not disclose the production of colonies of undifferentiated avian cells. Rather, Chang 1995 discloses culturing of PGCs under conditions wherein the PGC population expands, but colonies of undifferentiated avian cells are not produced.

Furthermore, the burden rests on the Patent Office to present evidence that the skilled artisan would be motivated to combine the teachings of the cited references to arrive at the combination claimed. Applicants respectfully submit that it

would not be possible to find such motivation as the understanding of the ordinary artisan at the time the application was filed was that PGCs isolated after stage 14 would be incapable of forming the claimed sustained culture.

The Patent Office, on the other hand, argues that Chang 1995 taught culturing cells isolated from the genital ridge at Stage 27 for 5 days. The instantly claimed sustained culture, however, is produced by isolating PGCs and stromal cells from a later than stage 14 embryo, and growing these cells to produce colonies of undifferentiated cells. Chang 1995 does not teach or suggest this, as described in more detail hereinabove.

The Patent Office asserts that the arguments presented during the prosecution of the instant application related to the current rejection are not persuasive because "Chang taught culturing cells isolated from the genital ridge at State 27 for 5 days". Applicants respectfully submit that this teaching is irrelevant because colonies of undifferentiated avian cells derived from PGCs do not form within this time period. Furthermore, applicants respectfully submit that the Chang 1995 reference must be viewed in its entirety. The cited reference was concerned with expanding a population of PGCs to increase their numbers, not with producing colonies of undifferentiated cells. Thus, applicants respectfully submit that one of ordinary skill in the art would not have sought to combine Chang 1995 and the '740 Patent because it was the understanding of the skilled artisan at the time of filing the instant application that later than stage 14 PGCs were destined for terminal differentiation into germ cells. Applicants respectfully submit that a skilled artisan attempting to produce a culture of undifferentiated cells would not employ cells believed to be committed to terminal differentiation.

And finally, applicants respectfully submit that the Patent Office's asserted motivation for combining the cited references is not relevant to the sustained culture as claimed in claim 44. The claimed sustained culture is not a culture of PGCs only. Rather, it is a culture comprising one or more colonies of undifferentiated avian cells, wherein the colonies are derived from the PGCs and are made up of cells each of which is characterized by a large nucleus, a prominent nucleolus, and little

cytoplasm. Applicants respectfully submit that under the conditions disclosed in Chang 1995, PGCs do not form colonies like those depicted in Figures 3 and 4 of the instant application. Rather, PGCs form loosely adherent single cells when plated onto feeder layers such as those disclosed in Chang 1995. This point is clearly disclosed in the cited reference itself on page 144, wherein it is stated that “PGCs on 5-day-old embryonic [germinal ridge stroma cells] were also counted after incubation for one day. After this stage, all the stroma cells were attached and spread on the culture surface and PGCs were loosely attached to the stroma cells and had a typical round, granular appearance” (emphasis added).

Thus, applicants respectfully submit that Chang 1995 teaches the use of avian stromal cells for increasing the numbers of PGCs. The subject matter of the instant claims does not relate to increasing PGCs numbers, however. Rather, the instant subject matter relates to a sustained culture comprising one or more colonies of undifferentiated avian cells. As a result, since Chang 1995 does not teach the use of avian feeder cells to produce one or more colonies of undifferentiated avian cells, applicants respectfully submit that Chang 1995 provides no motivation to use avian feeder cells instead of the mouse fibroblasts as taught in the ‘740 Patent.

Accordingly, applicants respectfully submit that a prima facie case of obviousness has not been made out, and as a result, applicants respectfully request that the rejection of claims 44, 47, 48, and 51-55 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 8-10 of the ‘740 Patent in view of Chang 1995 be withdrawn, and respectfully solicit a Notice of Allowance to that effect.

V.B. Rejection based on U.S. Patent No. 5,656,479 or 5,830,510
in view of Chang 1995

Claims 44, 47, 48, and 51-55 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,656,479 or 5,830,510 (hereinafter “the ‘479 Patent” and “the ‘510 Patent”, respectively) in view of Chang 1995. Applicants have carefully considered

the rejection and the Patent Office's bases therefor, and respectfully traverse the rejection as follows.

Applicants initially note that the discussion presented immediately above with regard to the rejection of claims 44, 47, 48, and 51-55 as obvious over the '740 Patent in view of Chang 1995 is applicable to the instant rejection. Summarily, none of the constituent patents that make up the "Petitte Patents" (*i.e.* the '740 Patent, the '479 Patent, and the '510 Patent) disclose the use of PGCs isolated from an avian embryo after stage 14 to produce a culture comprising colonies of undifferentiated avian cells. The Patent Office's burden is to demonstrate that one of ordinary skill in the art would have been motivated by the teachings of the cited references to create the claimed combination itself. Applicants have contended, and the Patent Office has acknowledged, that those of skill in the art believed that the PGCs used to generate the instantly claimed sustained cultures were believed to be incapable of forming undifferentiated avian cells expressing an embryonic stem cell phenotype (*i.e.* a large nucleus, a prominent nucleolus, and little cytoplasm). Thus, the art teaches away from the production of the instantly claimed combination, and thus, there could have been no motivation to employ PGCs isolated from after stage 14.

The Patent Office asserts that "the art does not teach away from the invention because Chang taught culturing cells isolated from the genital ridge at Stage 27 for 5 days". Official Action at page 17. Again, applicants respectfully submit that this is irrelevant because the cultures of Chang 1995 are cultures of PGCs only, not cultures of undifferentiated cells.

Furthermore, the Patent Office's assertion that "a culture sustained for 5 or 14 days is not structurally or functionally different than a culture sustained for one or two months as claimed" is unsupported by any competent scientific authority, and in this particular case, is not correct. The cultures claimed in the instant application are cultures that contain colonies of undifferentiated avian cells. These colonies of cells are not taught or suggested by Chang 1995. Chang 1995 discloses cultures of PGCs, which are large, granular cells. After 5 days in culture, the cells disclosed in Chang 1995 are still PGCs – they are large and granular. The instantly claimed

sustained culture, on the other hand, contains one or more colonies of undifferentiated cells. Thus, contrary to the Patent Office's assertion, the instantly claimed sustained culture is both structurally and functionally different than a culture sustained for 5 or 14 days because the latter cultures do not contain one or more colonies of undifferentiated cells.

Summarily, there is no motivation to combine Chang 1995 with the '479 Patent and/or the '510 Patent because Chang 1995 does not cure the deficiency of the '479 Patent and the '510 Patent that has been conceded by the Patent Office: culturing the PGCs on avian feeder cells. Since the '479 Patent and the '510 Patent do not disclose culturing the PGCs on avian feeder cells, and Chang 1995 does not disclose or suggest that culturing PGCs on avian feeder cells will result in the production of undifferentiated avian cells, applicants respectfully submit that the cited combination does not provide a motivation to use avian feeder cells in a sustained culture of avian cells to produce one or more colonies of undifferentiated avian cells as claimed in claims 44, 47, 48, and 51-55.

Accordingly, applicants respectfully submit that a *prima facie* case of obviousness has not been made out, and as a result, applicants respectfully request that the rejection of claims 44, 47, 48, and 51-55 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of either the '479 Patent or the '510 Patent in view of Chang 1995 be withdrawn. Applicants therefore respectfully submit that claims 44, 47, 48, and 51-55 are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

V.C. Rejection based on U.S. Patent No. 6,156,659 in view of Chang 1995

Claims 44, 47, 48, and 51-55 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,156,659 to Ponce de Leon et al. (hereinafter "the '569 Patent") in view of Chang 1995. Applicants have carefully considered the rejection and the Patent Office's bases therefor, and respectfully traverse the rejection as follows.

Initially, applicants respectfully submit that there is no common relationship of inventorship or ownership between the instant application and the '569 Patent as is required under M.P.E.P. 804 for an obviousness-type double patenting rejection. Accordingly, applicants respectfully request that the instant rejection be withdrawn.

Nonetheless, in an abundance of caution, applicants address the instant rejection as if it were a rejection under 35 U.S.C. § 103. The '569 Patent does not disclose the use of PGCs isolated from an avian embryo after stage 14. As discussed in more detail hereinabove, Chang 1995 also does not disclose producing colonies of undifferentiated cells from PGCs isolated after stage 14. Thus, applicants respectfully submit that the references cannot be combined to disclose or suggest creating sustained cultures of undifferentiated cells from PGCs isolated after stage 14.

The Patent Office also has the burden to demonstrate that one of ordinary skill in the art would have been motivated by the teachings of the cited references to create the claimed combination itself. Applicants have contended, and the Patent Office has acknowledged, that those of skill in the art believed that the instantly claimed cells were believed to be incapable of forming undifferentiated avian cells. Thus, the art teaches away from the production of the instantly claimed combination. Consequently, applicants respectfully submit that there could have been no motivation to employ PGCs isolated from after stage 14 to produce cultures containing colonies of undifferentiated avian cells.

Accordingly, applicants respectfully submit that a prima facie case of obviousness has not been made out, and as a result, applicants respectfully request that the rejection of claims 44, 47, 48, and 51-55 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of the '569 Patent in view of Chang 1995 be withdrawn. Applicants therefore respectfully submit that claims 44, 47, 48, and 51-55 are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

VI. Discussion of the New Claims

New claims 56-57 have been added. Support for the new claims can be found throughout the specification of the application as filed, including particularly at page 4, lines 10-17. Additional support for the amendments can be found on page 5, line 16, through page 7, line 24 (Brief Description of the Drawings), at page 12, lines 3-4, in Figures 1-4, and in Examples 1-4.

Applicants respectfully submit that the new claims are patentably distinguished from the cited references for the reasons set forth hereinabove with respect to amended claim 44. As claim 44 is believed to be distinguished from the cited references and the new claims depend directly or indirectly from claim 44, applicants respectfully submit that the new claims are also in condition for allowance. Applicants respectfully solicit a Notice of Allowance to that effect.

CONCLUSION

In light of the above Amendments and Remarks it is respectfully submitted that the present application is now in proper condition for allowance, and such action is earnestly solicited.

If any minor issues should remain outstanding after the Examiner has had an opportunity to study the Amendment and Remarks, it is respectfully requested that the Examiner telephone the undersigned attorney so that all such matters may be resolved and the application placed in condition for allowance without the necessity for another Action and/or Amendment.

Serial No.: 09/757,054

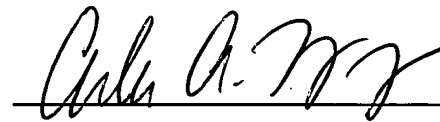
DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any deficiencies of payment or credit any overpayments associated with the filing of this Amendment After Final to Deposit Account No. 50-0426.

Respectfully submitted,
JENKINS, WILSON & TAYLOR, P.A.

Date: 02/07/2005

By: _____



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